Conforming to the ICH Guideline for the Photostability Testing of New Drug Substances and Drug Products (ICH Q1B) Using the Atlas SUNTEST® CPS+

This document summarizes the key requirements in the ICH Guideline and offers recommendations for operating the Atlas SUNTEST CPS+ with light monitor WB 300-800 nm

EXECUTIVE SUMMARY

"The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration." *From the official website for ICH, www.ich.org.*

The result of this effort was a guideline, the ICH Harmonized Tripartite *Guideline on Stability Testing of New Drug Substances and Products* (ICH Q1A). Photostability testing is further addressed in a separate official ICH document (ICH Q1B). This applies to both forced degradation stress testing and confirmatory studies of the active drug substance, drug product and excipients. ICH Q1B is applicable to small molecules; large molecules (proteins, monoclonal antibodies, etc.) are addressed in the separate document, *Stability Testing of Biotechnological/Biological Products* (ICH Q5C).Additionally the Q1B protocol has been adopted as the VICH Tripartite Harmonized Guideline covering the Photostability Testing of New Drug Substances and Products in the Veterinary Field.

Despite Implementation of the ICH stability and Photostability guidelines, issues remain that are not specifically covered in the documents and left to the researcher's discretion. Additionally, several non-equivalent options are available, reflecting different practices for handling drug products on different continents.

Atlas Material Testing Technology GmbH
Vogelsbergstraße 22 • 63589 Linsengericht-Altenhasslau
Phone: +49-6051-707-0 • Website: www.atlas-mts.com • Email: atlas.info@ametek.de

SUMMARY OF KEY Q1B CONTENTS*

**The numbers and letters correspond to the sections of the official ICH Q1B document; however, not all sections are listed.*

1. General

The ICH Harmonized Guideline on Stability Testing of New Drug Substances and Products requires that photostability testing be an integral part of stress testing. The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that light exposure does not result in unacceptable change.

B. Light Sources, Option 1

ICH recommends the following light sources that emit an output similar to D65/ID65 emission standard. "D65 is the internationally recognized emission standard for outdoor daylight as defined in ISO 10977:1993 standard. ID65 is the equivalent indoor indirect daylight standard[(1)]." Light sources conforming to D65/ID65 emission standard should contain UV and visible spectrum, such as:

- Xenon lamps
- Artificial daylight fluorescent lamp combining visible and UV outputs
- Metal-halide lamps

C. Procedure

ICH requires the following two exposure criteria for confirmatory photostability studies:

- Not less than 1.2 million Lux hours of Visible (400-800 nm) exposure
- Not less than 200 Watt•hours / m² of UV (320-400 nm) exposure

The ICH Guideline states that "The minimum Visible light exposure level represents approximately 3 month of continuous exposure to artificial visible light in the pharmacy, warehouse or home with the protective container removed from the product. The UV light exposure roughly corresponds to 1 to 2 days inside close to a window with sunlight exposure[(2)]." However, the ratio of UV to VIS radiation that the ICH estimates to represent the "real" storage conditions differs from the UV/VIS ratio defined in the standard for indoor direct daylight (ID65). ID65 is generally selected as more representive of actual exposure conditions; however, the more severe D65 conditions may be useful for "forced degradation" studies.

[1,2] S.R. Thatcher, R.K. Mansfield, R.B. Miller, C.W. Davis, and S.W.Baertschi, "A Technical Guide and Practical Interpretation of the ICH Guidelines and Its Application to Pharmaceutical Stability." *Pharmaceutical Technology*, March 2001: 102.

OPTION 1 XENON LIGHT SOURCE

Filtered (D65 or ID65) xenon discharge lamps are full-spectrum light sources and simultaneously expose in the UV, Visible and IR spectral regions.

Because the spectral distribution of the selected radiation source must conform to the D65 or ID65 standard (Option 1), a total irradiance of 200 W•hours/m² in the UV region (320-400 nm) simultaneously underexposes the visible by ca. 60%, and a total irradiance of 1.2 million Lux-hours in the Visible (400-800 nm) simultaneously overexposes the UV by ca. 240%.

At present, no single source provides the combination of simultaneous UV and Visible exposure levels required by the ICH Q1B (D65/ID65) without overexposure to the UV or underexposure to the Visible. However, since the recommended exposures are ***minimums***, exceeding the minimum exposure in the UV or Visible is perfectly acceptable.

Overexposure can be avoided by (1) excluding the excess of UV radiation by the use of UV blocking filters around the specimen upon reaching the desired UV dose; (2) remove one half of the specimens after reaching the UV dose and continuing exposure to the Visible dose on the remaining specimens; or (3) running two separate tests, one for each criterion (UV and Visible), with identical specimens. Exceeding the minimum UV dosage is acceptable according to the guidelines, and may actually be a better simulation of end use conditions where the product is exposed to direct daylight or daylight filtered through window glass.

The Atlas SUNTEST® meets the ID65 spectral criterion with an optical filter system consisting of a **coated** quartz dish (standard feature) + a window glass filter (accessory) + an ID65 filter (accessory). The SUNTEST filtered xenon light source is a full spectrum light source containing both UV and Visible outputs as required in Option 1, with a UV cut-on of approx. 320 nm and a spectral distribution corresponding to ID65 per ISO 10977 (Graphic 1).

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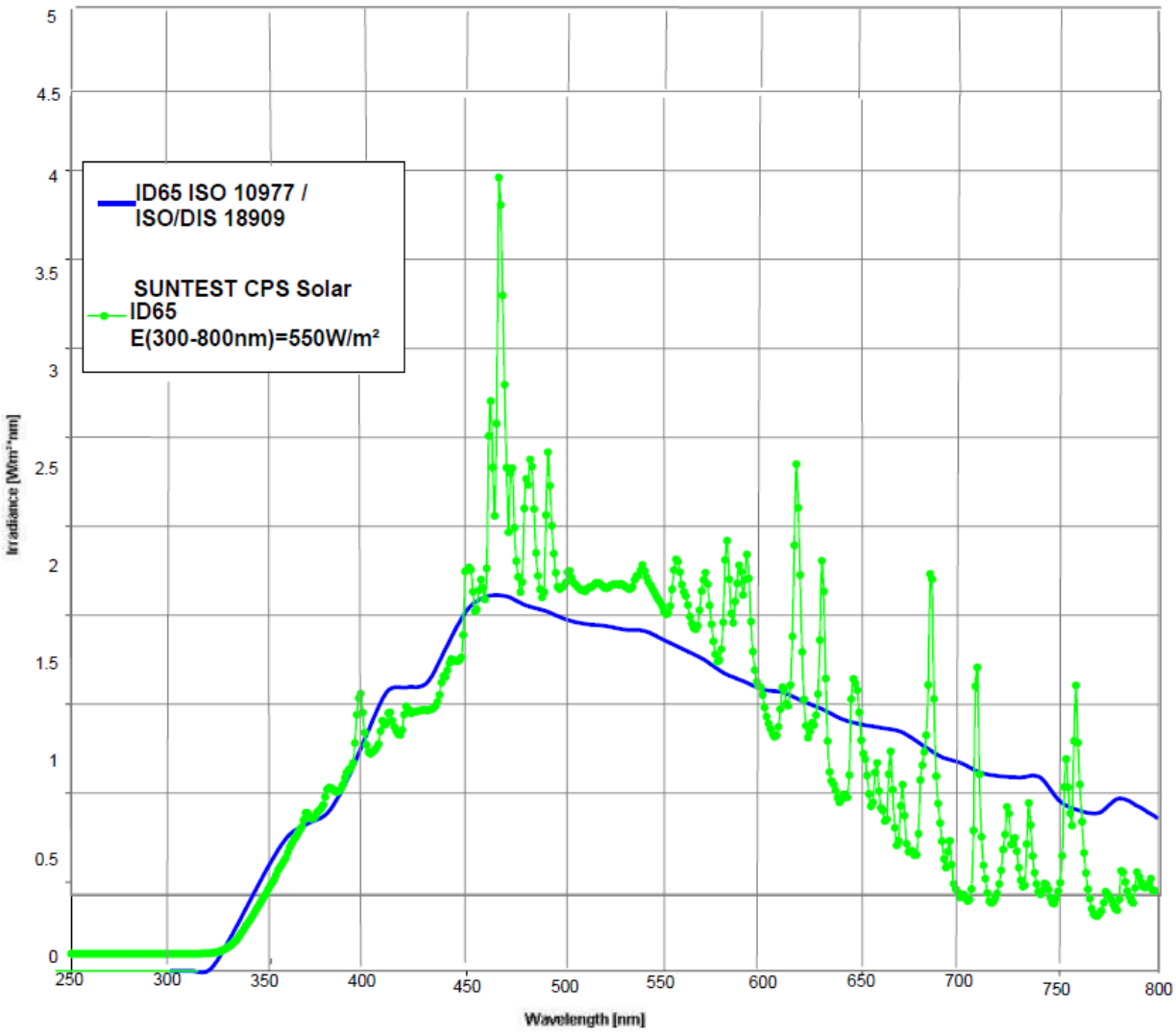
The following filter set is required to provide ID65 for the SUNTEST CPS+:
In addition to the coated quartz dish (coated quartz = base filter, functioning as carrier for optical filters)

P/N 56052372	Window glass filter, simulating exposure behind 3 mm window glass
P/N 56077769	Solar ID65, cut-on at 320 nm, 3 mm

Graphic 1: Spectrum Comparison between ID65 (ISO 10977 / ISO DIS 18909) and SUNTEST CPS+ with Solar ID65 filter system



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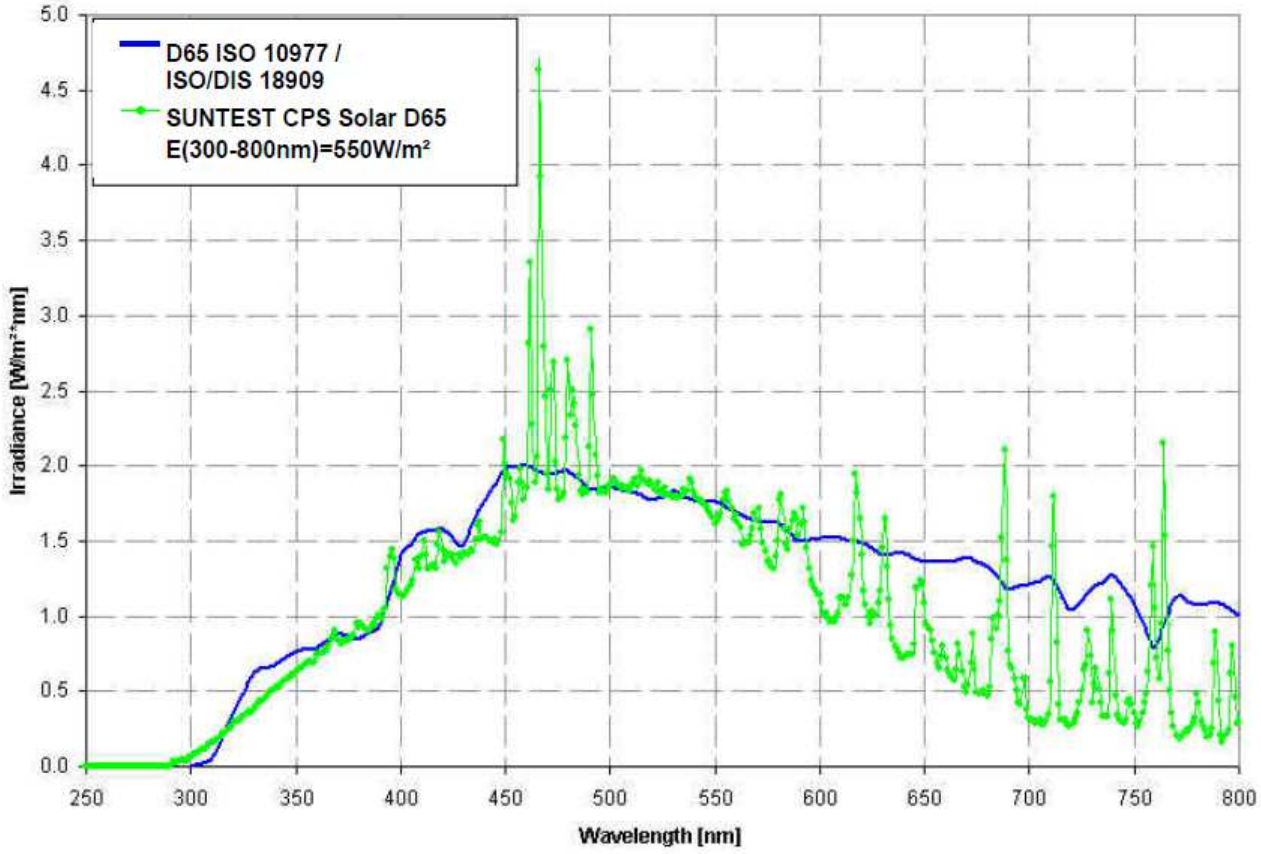
The following filter set is required to provide the more severe Daylight D65 for the SUNTEST CPS+: In addition to the coated quartz dish (coated quartz = base filter, functioning as carrier for optical filters)

P/N 56052371	Daylight filter (Special UV glass), cut-on at ca. 290 nm, simulating solar radiation outdoors

Graphic 2: Spectrum Comparison between D65 Daylight (ISO 10977 / ISO DIS 18909) and SUNTEST CPS+ with Daylight filter system



DETERMINING TEST DURATION

The test procedures mentioned previously describe *minimum* exposure levels for confirmatory testing. Exposure dosage in the Atlas SUNTEST CPS+ is measured in radiometric units (Kilojoules in a range of 300-800nm) or can be switched to Lux control, enabling exposure dosage in Kilolux in the visible range.

Exposure duration may be expressed in chronological time (hours). Remember, exposure duration is dependent on the irradiance (light intensity) settings.

Radiation (Dosages) for CPS+; light monitor **WB300-800 nm** (allowing also Lux control):

1) UV minimum requirement

- 200 Watt•hours/m² is approximately 8000 KJ/m² (300-800 nm)

2) VIS minimum requirement

- 1.2 million Lux•hours is approximately 24060 KJ/m² (300-800 nm)

Based on an irradiance level between 300-800 nm, the irradiance level between 320-400 nm can be approximated by the following equation (for ID65):

W/m² (320-400 nm) = W/m² (300-800 nm) ÷ 11.5

The illuminance level in Kilolux (klx) can be approximated by the following equation (for ID65):

1 klx = 4.4 W/m² (300-800 nm)

SUNTEST CONDITIONS FOR THE ICH Q1B PROTOCOL

1. Filters

The ID65 requirements in the ICH guideline can be achieved by using the SUNTEST ID65 filter system as described on page 4.

2. Irradiance and Exposure Duration

The ICH guideline does not recommend a specific irradiance (light intensity) setting. The SUNTEST with the above filter system can accommodate a range of irradiance values from a minimum of 250 W/m^2 in the wavelength range of 300-800 nm to a maximum of 765 W/m^2 in the wavelength range of 300-800 nm. Lux, as used in the ICH guideline, is a photometric intensity unit for the visible bandwidth between ca. 400-800 nm, weighted to the spectral response of the human eye. Higher irradiance settings result in shorter test durations to reach a given exposure. However, from a practical consideration, higher irradiance results in higher chamber air and specimen temperatures because the xenon emission includes infrared radiation.

The following provides an estimation of test durations at minimum and maximum SUNTEST CPS+ irradiance levels to reach the minimum exposure requirements:

1) The UV minimum requirement: 200 Watth/m² (between 320-400 nm):

- At minimum irradiance: 200 Wh/m² ÷ 21.7 W/m² * = 9.2 h SUNTEST CPS+ exposure

  **** (250 W/m² ÷ 11.5)***

- At maximum irradiance: 200 Wh/m² ÷ 66.5 W/m² **= 3,0 h SUNTEST CPS+ exposure

  ***** (765 W/m² ÷ 11.5)***

2) The Visible minimum requirement: 1.2 million Lxh (between ca. 400-800 nm):

- At minimum irradiance: 1200 klxh ÷ 56.6 klx * = 21.2 h SUNTEST CPS+ exposure

  **** (250 W/m² ÷ 4.4)***

- At maximum irradiance: 1200 klxh ÷ 174 klx ** = 6,9 h SUNTEST CPS+ exposure

  ***** (765 W/m² ÷ 4.4)***

- At maximum illuminance: 1200 klxh ÷ 150 klx *** = 8,0 h SUNTEST CPS+ exposure

  ****** maximum instrument setting for klx = 150 klx***

**** Note: SUNTEST CPS+ (II) (Model 2012) allows control in Lux, too. Programming and setting the Visible minimum requirement - 1,2 Mlxh (1200 klxh) as a dosage is possible.*

Alternatively, exposure times for the above minimum requirements for UV or Visible depend on the irradiance (light intensity). The SUNTEST CPS+ with light monitor WB300-800 nm has an irradiance operating range of 250 W/m² to 765 W/m² in the wavelength range of 300-800 nm.

3. Temperature

Determining thermal stability of drug substances and products is a separate requirement and is conducted independently from the photostability portion of the ICH guideline.
However, the infrared energy emitted from the xenon lamp causes the chamber temperature to rise above the ambient temperature. ICH Guideline Q1B requires that care be taken to avoid degradation of thermally labile products. To avoid excessive temperatures, Atlas recommends using the optional Atlas SunCool air chiller to achieve lower test chamber and black standard temperatures. Using the SunCool even at maximum irradiance will allow 30% to 45% lower temperatures than using the SUNTEST by itself (typical chamber air temperature in the range of ca. 30 °C).

The SUNTEST uses a Black Standard Thermometer (BST) to regulate air temperature conditions in the exposure chamber. The BST is a widely used surface temperature probe for monitoring maximum possible surface temperature of a black surface. To achieve the ambient temperature requirement, Atlas recommends setting the BST to 0 °C. The 0 °C setting of BST will activate the Atlas SunCool, which will provide the chamber air temperature of near ambient condition, approximately 15 °C to 20 °C depending on irradiance and laboratory conditions.

Note that photo-degradation rates should increase linearly with the photon flux (irradiance intensity) while thermal degradation rates will not increase linearly with increasing temperature, but rather will follow typical Arrhenius kinetics. Therefore, more thermal degradation can occur in a longer test at lower irradiance and temperature than at higher once.

Forced Degradation Tests

The ICH Guideline states that the purpose of "forced degradation" studies is to evaluate the overall photosensitivity of the material for method development purposes and/or to elucidate the degradation pathways and to validate stability-indicating assays. Unlike conformance testing, no specific testing criteria or minimums are recommended. However, the forced degradation experiment on the drug substance should be conducted using a visible light and UV exposure in excess of that used for formal product testing (e.g., by a factor of 3- to 5-fold). Alternatively, exposure may be continued until significant degradation has occurred. These studies are usually conducted on solid drug substances and also on solutions that are usually more susceptible to degradation.

Calibration

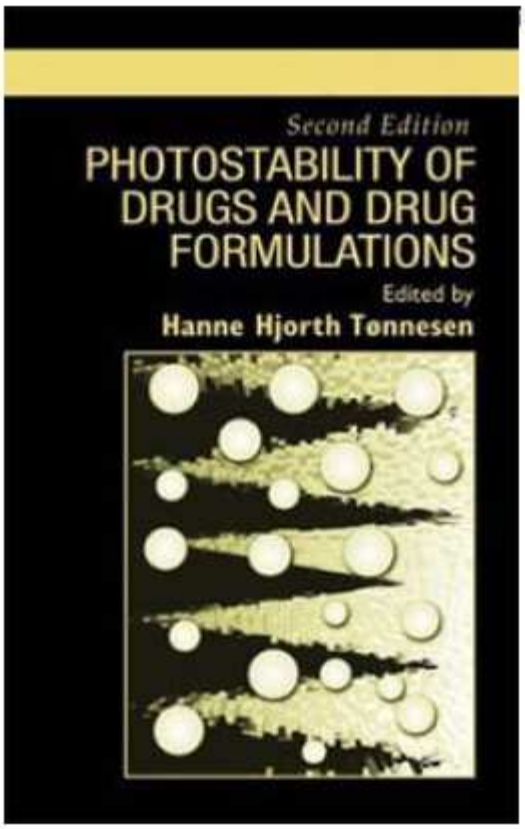
As chemical actinometers have shown inaccuracies, it is advised to calibrate the SUNTEST with approved radiometers (e.g. SunCal™). Best laboratory practice would dictate that calibration of any device be verified before and after each test. However, due to the stability of the integral radiometer measuring system of the SUNTEST CPS+, common practice is to have the SUNTEST CPS+ calibrated at intervals of 6 or 12 months by an accredited, Atlas-authorized service representative (check for local availability of ISO 17025 accreditation). The Certificate of Calibration issued by Atlas-authorized service is valid for one year; if the equipment is moved to another location or the electrical supply is changed, Atlas recommends recalibration.

Cautionary Note: Radiometers and spectroradiometers must be calibrated for the specific type of lamp and power supply. Atlas manufactures specific SunCal™ irradiance calibrators for use with SUNTEST and other Atlas instruments and the use of third-party devices may result in inaccurate measurements and calibrations.

Further Information

A more thorough discussion of photostability testing and the ICH Q1B Guideline can be found in: Photostability of Drugs and Drugs Formulations 2nd edition, edited by Hanne Hjorth Tonnesen, CRC Press, ©2004, www.crcpress.com.

A summary of Q1B photostability testing may be found in: S.R. Thatcher, R.K. Mansfield, R.B. Miller, C.W. Davis and S.W.Baertschi, *"A Technical Guide and Practical Interpretation of the ICH Guideline and Its Application to Pharmaceutical Stability" Part 1 & 2.* Pharmaceutical Technology, March & April 2001.



For more information on the Atlas SUNTEST® CPS+ or XLS+ Photostability Testing Equipment, please visit us at
www.atlas-mts.com

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